Content available at: https://www.ipinnovative.com/open-access-journals

IP Journal of Diagnostic Pathology and Oncology

Journal homepage: https://www.jdpo.org/

Case Report

Multiple-lesion, non-familial basal cell carcinoma-An interesting oddity

Kirti G Pardeshi[1], Hoogar Mallinath Basalingappa[1], Satish Bhasale[1], Sameer Arun Kadam[2]*, Vaishali Bhonsle[1], Nakul Sampat[1], Arvind Valand[1]

[1] *Vedantaa Insitute of Medical Sciences, Dahanu, Maharashtra, India*
[2] *Dept. of Pathology, Vedantaa Institute of Medical Sciences, Dahanu, Maharashtra, India*

ARTICLE INFO

Article history:
Received 22-08-2023
Accepted 05-10-2023
Available online 05-12-2023

Keywords:
Basal cell carcinoma
multilesion BCC
nonsyndromic BCC
nonfamilial BCC
multiple Basal cell carcinomas
Gorlin syndrome
nevoid basal cell carcinoma

ABSTRACT

Basal cell carcinoma (BCC) is the most common primary carcinoma of skin, which accounts for three-fourth of all primary skin tumours. Basal carcinoma occurs commonly as a single lesion, though occasionally it can occur as Multiple lesions, which may occur in close association with heredofamilial conditions such as nevoid basal cell carcinoma syndrome (Gorlin's syndrome), Bazex syndrome, Rombo syndrome, and unilateral basal cell nevus syndrome.

The case of multiple basal cell carcinomas being presented here is unique in its occurrence inasmuch as it is not associated with heredofamilial conditions, and despite not being associated with heredofamilial conditions there is occurrence of multiple basal carcinomas in a patient in a tertiary care hospital in a dominantly tribal region. The patient has no family history of genodermatosis that could increase the incidence of multiple basal cell carcinomas such as xeroderma pigmentosum, and no history of other predisposing conditions including actinic keratosis, Bowen's Disease, leukoplakia, Erythroplasia of Queyrat, keratoacanthoma, radiation dermatitis and exposure to arsenicals, psoralen and other photosensitizing medications. However, the patient had history of having raised macules over the face which were diagnosed as seborrheic keratosis.

1. Introduction

Basal cell carcinoma (BCC), known by various synonyms such as 'Basalioma', 'Basal cell epithelioma', 'Rodent ulcer', 'Jacobs' ulcer', was described in 1924.[1] Among skin cancers basal cell carcinoma forms the bulk of the primary malignant tumours, which comprises 75 per cent of all skin cancers and it is the most common malignancy among Caucasians.[1–3] Basal cell carcinoma occurs mainly on the sun-exposed areas.[1] Rarely it can occur in mucous membrane and skin of palms and soles.[4] The incidence of basal cell carcinoma varies from one geographical area to another with incidence being two per 100,000 population in east Asia to 1600 per 100,000 population per year in Queensland, Australia.[2] The overall age and sex standardized annual incidence in Minnesota, USA, was reported at 146 per 100 000.[5] The incidence of basal cell carcinoma is more common in males over 40 years than in females with mean age at diagnosis being 68 years with male to female ratio being approximately 1.5 to 2:1.[6–8] Individuals with blonde hair, blue eyes have increased risk of developing basal cell carcinoma.[5,7,9–17]

Basal cell carcinoma is a slow-growing tumor of non-keratinizing cells originating in the basal layer of interfollicular epidermis.[2] It is rarely metastasizing tumour with the rate of metastasis being <0.1 per cent. It generally occurs in skin in sun-exposed areas as a single lesion. The factors contributing to the risk of

* *Corresponding author.*
E-mail address: sak77kadam.sk@gmail.com (S. A. Kadam).

https://doi.org/10.18231/j.jdpo.2023.053

developing basal cell carcinoma include exposure to arsenic or predisposing conditions like actinic keratosis, Bowen's Disease, leukoplakia, Erythroplasia of Queyrat, keratoacanthoma, radiation dermatitis, and xeroderma pigmentosum.[3–11,18–22]

Basal cell carcinoma especially multiple-lesion basal cell carcinomas occur in association with variety of heredofamilial conditions such as nevoid basal cell carcinoma syndrome (Gorlin's or Gorlin-Goltz syndrome),[1–14,18–22] Bazex syndrome, Rombo syndrome, and unilateral basal cell nevus syndrome.[9] The case being presented here is of multiple-lesion, non-Gorlin syndromic BCC associated with seborrheic keratosis.

2. Case Report

A 65 year-old male, a farmer by occupation, presented with history of swellings over left cheek just below eyelid and over the forehead. On examination, growth over left cheek was slightly polypoidal and pedunculated. The swelling over the forehead was sessile and globular. The growth over left cheek was clinically diagnosed provisionally as? *BCC and the swelling over the* forehead region was clinically diagnosed as lipoma. Additionally, the patient also Had multiple, slightly raised macules over the face around the nasolabial fold and Cheek region, which were clinically diagnosed as lesions of Seborrheic keratosis.

The histopathology section of the tertiary care hospital received two specimens in two separate containers labelled separately denoting as swelling over the cheek and forehead, respectively.

2.1. Gross examination

On gross examination, the growth over the left cheek was polypoidal in nature and measured 3x2x1 cm in size. Cut section of the growth was grey white with focal areas of hemorrhage. The swelling over forehead was skin-colored, and globular in morphology, soft to firm in consistency, and measured 2 cm in diameter. Cut section of the swelling revealed diffusely yellowish areas. Representative tissue sections were submitted for processing. Tissue sections were processed as per the standard tissue processing method and stained with Hematoxylin and Eosin.

2.2. Microscopic examination

Sections from the polypoidal growth and swelling over the left cheek region showed epidermis lined by keratinizing stratified squamous epithelium with the subjacent dermis showing multiple discrete nests and sheets of cells separated by fibrous septa. At places, the neoplastic cells form nodular aggregates and cell nests with microcystic areas. The dermis showed a tumor arranged in nodular and focal micro cystic pattern composed of basaloid cells with nuclear palisading at the periphery and surrounding stromal retraction.

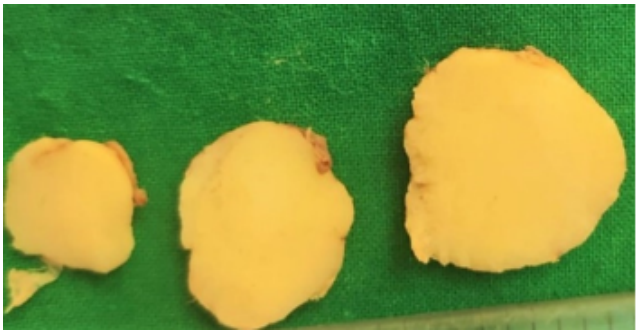

Figure 1: Gross photograph of cut section of lesion over forehead, showing diffusely yellowish areas

Sections from the forehead swelling showed nodular aggregates, islands and sheets of basaloid cells rimmed at the periphery by neat arrangement of cells with nuclear palisading. In some areas the nodular aggregates were interspersed by hyalinised collagen bundles giving an appearance of cribriform pattern. Also noted were nests and sheets of cells separated by deeply eosinophilic basement membrane like material. With above histopathological findings a diagnosis of Basal cell carcinoma with focal trichoepitheliomatous differentiation was made. The patient was further referred to higher center for additional investigations for categorization of Basal cell carcinoma. However, patient was lost in follow up.

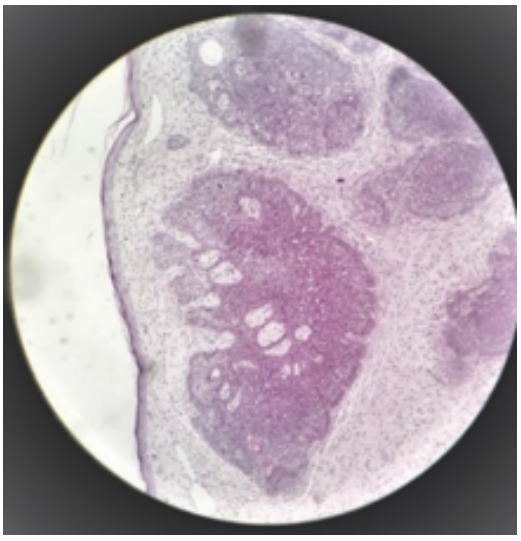

Figure 2: Photo micrograph showing basaloid cells with nuclear palisading in periphery and surrounding stromal retraction (H and E, 10x)

3. Discussion

Basal cell carcinoma is the commonest cancer, which can occur as a single lesion on the face and neck. Although

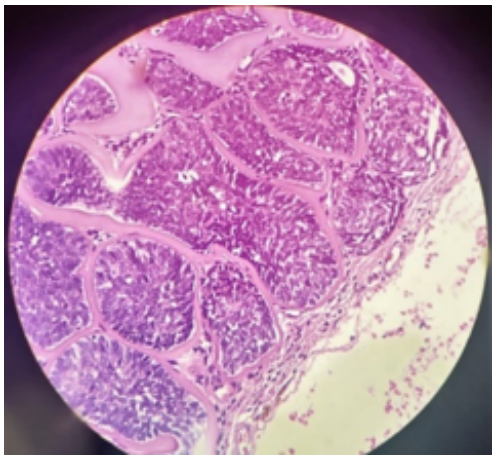

Figure 3: Photo micrograph showing basaloid cells with nuclear palisading in periphery and surrounding stromal retraction, (H and E, 40x)

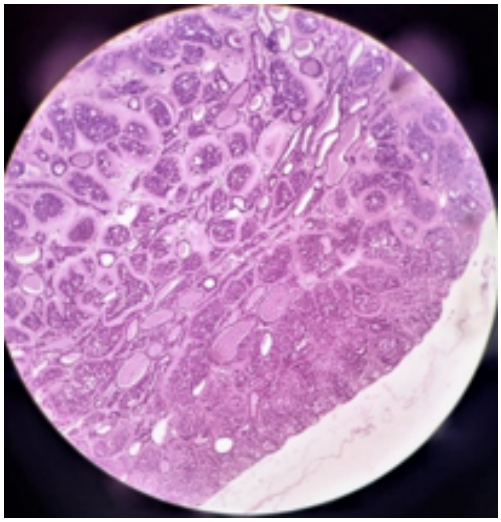

Figure 4: Photo micrograph showing aggregates of basaloid cells separated by delicate hyalinised stroma (H and E, 10x)

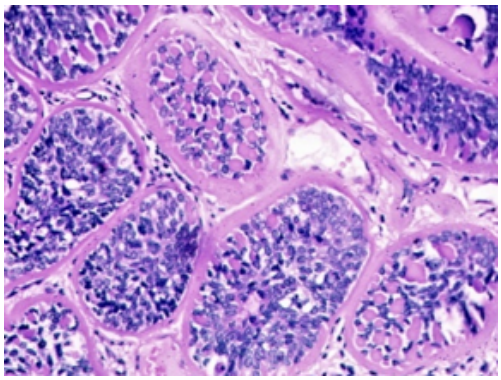

Figure 5: Photo micrograph showing aggregates of basaloid cells separated by delicate hyalinised stroma (H and E, 40x)

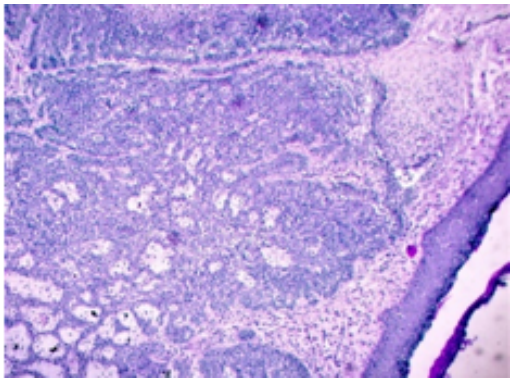

Figure 6: Photo micrograph showing nests and sheets of cells separated by deeply eosinophilic basement membrane like material (H and E, 40x)

multiple-lesion basal cell carcinoma is not common, 36-50 percent cases of basal cell carcinoma have an increased risk of developing additional BCC after the first lesion within 5 years.[7,8] The recurrence rate of BCC is variable; when the tumor is completely excised, the recurrence rate is between 5 per cent and 14 per cent.[18]

Basal cell carcinoma can be classified in different ways. One of the classifications categorizes BCC into sporadic (nonsyndromic) and syndromic (hereditary) forms.[2,14] In the sporadic group of basal cell carcinoma, individuals having BCC do not have any genodermatosis which make them predisposed to get cutaneous malignant tumours. In the second group (syndromic group), individuals are affected with genetic skin disorders (Grolin-Goltz syndrome, Bazex syndrome, xeroderma pigmentosum) which makes them susceptible to develop BCC at an early age. As studied widely, one of the striking features of BCC is its variation in its presentation in sites, number of lesions and its accrual or occurrence of number of tumors per year from the first presentation.[2,14–17]

Another classification proposed by Ramachandran et al[15] is based on the number of lesions at presentation. It categorizes BCC into single presentation phenotype (SPP) or multiple presentation phenotypes (MPP).[15–17]

SPP can be further subdivided into categories of SPP-one and SPP-more. SPP-one comprises patients with only a single BCC lesion at first presentation with no additional lesions. SPP-more group included patients with only one primary BCC lesion at first presentation but the development of additional single lesions during the follow-up period. MPP was subdivided into MPP-cluster initially and MPP-cluster later. A cluster was defined as the presence of two or more new primary BCC lesions at the same locality. MPP-cluster initial includes patients who present with a cluster of BCC lesions at first presentation but may or may not develop additional BCC during follow-up. MPP-cluster-later comprises patients who had only 1-primary

BCC lesion at the first presentation but developed a cluster at a subsequent presentation. Although this classification can be adapted, it had limitations as the development of BCC lesions is a dynamic process over a long period with changes in appropriate categories. Additionally, patients with a single lesion may die before adequate follow-up.[15]

The risk factors involved in development of BCC include sensitization of skin by photosensitizing medications such as tetracycline, thiazide diuretics, non-steroidal anti-inflammatory drugs (NSAIDs), retinoid and antimicrobial agents such as tetracycline, which cause phototoxic or photo allergic reactions when exposed to ultraviolet (UV) light, which leads to predisposition of skin to UV-induced damage. The use of anti-microbial agents, particularly tetracycline for the treatment of acne in adolescence along with increased UV-exposure during this active age-group is known to be associated with increased risk of BCC in adults.[2,6]Of the various risk factors, UV light is a major risk factor triggering mutations in tumor suppressor genes. Ionizing radiation, arsenic, and polyaromatic hydrocarbons play an important role in causing mutation in regulatory genes and alteration in immune surveillance.[6] UV-induced mutations in p53 such as C-C and T-T nucleotide bases in pyrimidine sites are demonstrated to occur in up to 60 per cent of BCC cases. Despite BCC having low metastatic potential, it is aggressive locally and tends to grow and infiltrate in tissues with a path of least resistance.[6]BCC usually metastases to the lung, lymph nodes, esophagus, oral cavity, and skin. Clinical variants of BCC are superficial, nodular, morphea form pigmented, fibro-epithelioma of Pinkus, and cystic BCC. Histological subtypes of BCC include superficial, nodular, micronodular, and infiltrative BCC.[14]

The fundamental genetic alterations involved in predisposition to BCC development, especially of multiple tumor development, are not yet clearly understood, but the changed genetic background greatly modulates response of skin to ultraviolent radiation [UVR]. The quintessential effectiveness of DNA reparative mechanisms definitely modifies the entire pathogenetic mechanism of BCC carcinogenesis. Over the years reduced DNA repair capacity (DRC) to repair UVR-induced DNA damage is proven as an independent risk factor for the development of BCC.[2,5] It is found that the DRC is significantly lower in patients suffering from BCC compared with control subjects, irrespective of biological behavior of the tumour, however it is curious to note that the same is seen among individuals having more than one BCC lesion. Most other studies point to the fact that there may be an effect of genetic alterations in a variety of molecular markers such as carcinogen-metabolizing enzymes, cell-signaling proteins on individuals becoming susceptible BCC.[5,15–17] Thus, various studies have demonstrated a close link between glutathione S-transferase, reduced nicotinamide adenine dinucleotide NAD, quinone oxidoreductase; cytochrome P450, vitamin D receptor, tumour necrosis factor alpha, and the protein patched homolog (PTCH) gene polymorphisms and the development of BCC, and the rate of development of BCC in respect to their number and accrual of lesions in individuals affected with BCC.[15–17,23,24]

One of the genetic pathways responsible for development of multi-lesion BCC is Nevoid basal cell carcinoma syndrome, an autosomal dominant disorder that is characterized by multiple BCCs, broad nasal root, borderline intelligence, jaw cysts, palmar pits, bilamellar calcification of falx cerebri, and multiple skeletal abnormalities in addition to hundreds of BCC.[8–17,21–23] The gene involved is located on chromosome 9q22.3. known as Patched gene or PTCH gene, it is a tumour suppressor gene, and in normal individuals it inhibits signal transduction in downward genes. In individuals with BCC, mutations in the gene lead to suppression of PTCH receptor to which sonic hedgehog (SHH) binds. This removes suppression of Smoothen protein, which acts as proto-oncogene leading to activation of transduction pathway through downward genes. This downward activation of transduction signaling activates various nuclear transduction genes. This is the molecular basis of development of multi-lesion BCC, which forms the basis of targeted therapy by using drugs such as Vismodegib, which does not have severe adverse drug reactions or long term side effects. The other ways of clinical management of BCC include surgical and non-surgical methods. The surgical methods of treating BCC are excisional surgery, curettage, cautery, cryosurgery and Mohs micrographic surgery, while non-surgical methods include radiotherapy, photodynamic therapy, topical use of fluorouracil and imiquimod.[25,26]

4. Conclusion

The multiple-lesion basal cell carcinoma case being presented here is one of its own kind in that it is reported from a predominantly tribal region in a patient who does not have family history of heredofamilial conditions that predispose to occurrence of multiple-lesion basal cell carcinoma nor the patient has nevoid basal cell carcinoma syndrome or Gorlin's syndrome which plays a role in occurrence of multiple-lesion basal cell carcinoma. However, the present case of multiple-lesion basal carcinoma is associated with seborrheic keratosis, the association of which is not known to be associated with multiple-lesion basal cell carcinoma as per the available medical literature.

Individuals with first lesion basal cell carcinoma have tendency to develop multiple basal cell carcinomas in the course of the disease and such first lesion of basal cell carcinoma has to be selected carefully for risk factor profile analysis and close clinical follow-up with periodic screening of any suspicious lesion resembling BCC for early detection

of imminent multi-lesion basal carcinoma for early and effective clinical management.

5. Conflicts of Interest

None.

6. Source of Funding

None.

References

1. Tilli CM, Van Steensel M, Krekels GA, Neumann HA, Ramaekars FC. Molecular etiology and pathogenesis of BCC. *Br J Dermatol*. 2005;152(6):1108–24.
2. Bartos V. Development of Multiple-Lesion Basal Cell Carcinoma of the Skin: A Comprehensive Review. *Sisli Etfal Hastan Tip Bu*. 2019;53(4):323–8.
3. Elder DE, Massi D, Scolyer RA, Willemze R. WHO Classification of Skin Tumours, 4th edn. France: International Agency for Research on Cancer; Lyon; 2018. p. 26.
4. Balakrishnan S. Basal cell carcinoma - Pathology. *J Skin Sex Transm Dis*. 2022;4(2):164–70.
5. Wong CSM, Strange RC, Lear JT. Basal cell carcinoma. *BMJ*. 2003;327(7418):794–8.
6. Marzuka AG, Book SE. Basal cell carcinoma: pathogenesis, epidemiology, clinical features, diagnosis, histopathology, and management. *Yale J Biol Med*. 2015;88(2):167–79.
7. Lara F, Santamaría JR, Garbers LE. Recurrence rate of basal cell carcinoma with positive histopathological margins and related risk factors. *An Bras Dermatol*. 2017;92(1):58–62.
8. Kiiski V, Vries E, Flohil SC, Bijl MJ, Hofman A, Stricker BHC, et al. Risk factors for single and multiple basal cell carcinomas. *Arch Dermatol*. 2010;146(8):848–55.
9. Loh T, Cohen PR. Red Dot Basal Cell Carcinoma: An Unusual Variant of a Common Malignancy. *J Drugs Dermato*. 2016;15(5):645–7.
10. Ahn SK, Lee HS, Han K, Lee SH, Lee S. Multiple BCC associated with keratocanthoma. *Yonsei Med J*. 1992;33(3):277–80.
11. Malhotra AK, Gupta S, Khaitan BK, Verma KK. Multiple basal cell carcinomas in xeroderma pigmentosum treated with imiquimod 5% cream. *Pediatr Dermatol*. 2008;25(4):488–91.
12. Lü Y, Zhu H, Ye W, Zhang M, He D, Chen W, et al. A new mutation of PTCH gene in a Chinese family with nevoid basal carcinoma syndrome. *Chin Med J (Engl)*. 2008;121(2):118–21.
13. Alghamdi Y. Skin tags as a presenting sign of basal cell nevus syndrome in three sisters of the same family. *Ann Saudi Med*. 2008;28(2):132–4.
14. Pankaj C. Non syndromic Multiple BCC. *Int J Head Neck Surg*. 2010;1(1):25–8.
15. Ramachandran S, Fryer AA, Smith AG, Lear JT, Bowers B, Griffith CE, et al. Basal cell carcinoma. *Cancer*. 2000;89(5):1012–8.
16. Ramachandran S, Freyer AA, Strange RC. Genetic factors determining cutaneous basal cell carcinoma phenotype. *Med Pediatr Oncol*. 2001;36(5):559–63.
17. Ramachandran S, Freyer AA, Smith A, Lear J, Bowers B, Jones PW, et al. Cutaneous basal cell carcinomas: distinct host factors are associated with the development of tumors on the trunk and on the head and neck. *Cancer*. 2001;92(2):354–8.
18. Nikam B, Kshirsagar A, Shivhare P, Garg A. Familial Multiple Basal Cell Carcinoma (Gorlin's Syndrome): A Case Report of a Father and Son. *Indian J Dermatol*. 2013;58(6):481–4.
19. Agarwal A, Raja A, Mahalingam S, Murhekar K. Multiple adenoid basal cell carcinoma: An uncommon presentation. *Indian J Dermatol Venereol Leprol*. 2019;85(4):393–6.
20. Čeović R, Smolković N, Pašić A, Kostović K, Hrsan D. Multiple basal cell carcinomas of lower legs with stasis dermatitis: a therapeutic challenge. *Acta Dermatovenerol Croat*. 2012;20(3):19–6.
21. Gorlin R. Nevoid basal cell carcinoma (Gorlin) syndrome. *Genet Med*. 2004;6:530–9. doi:10.1097/01.GIM.0000144188.15902.C4.
22. Wong AH, Leung AKC, Barankin B. Sclerosing Basal Cell Carcinoma. *Int J Clin Med Imaging*. 2015;2(4):1000315. doi:10.4172/2376-0249.1000315.
23. Robinson JK. Risk of developing another basal cell carcinoma. A 5-year prospective study. *Cancer*. 1987;60(1):118–20.
24. Lear JT, Tan BB, Smith AG, Bowers W, Jones PW, Heagerty AH, et al. Risk factors for basal cell carcinoma in the UK: case-control study in 806 patients. *J R Soc Med*. 1997;90(7):371–4.
25. Hextall FB, Perkin W, Bong J, William HC. Interventions for Basal Cell Carcinoma of skin. *Cochrane Database Syst Rev*. 2007;24(1):CD003412. doi:10.1002/14651858.CD003412.
26. Cowey CL. Targeted Therapy for advanced BCC Vismodegib and beyond. *Dermatol Ther (Heidelb)*. 2013;3(1):17–31. doi:10.1007/s13555-013-0019-9.

Author biography

Kirti G Pardeshi, Associate Professor

Hoogar Mallinath Basalingappa, Associate Professor

Satish Bhasale, Assistant Professor

Sameer Arun Kadam, Assistant Professor

Vaishali Bhonsle, Professor

Nakul Sampat, Senior Resident

Arvind Valand, Professor

Cite this article: Pardeshi KG, Basalingappa HM, Bhasale S, Kadam SA, Bhonsle V, Sampat N, Valand A. Multiple-lesion, non-familial basal cell carcinoma-An interesting oddity. *IP J Diagn Pathol Oncol* 2023;8(4):225-229.